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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,745	CASIMIR, COLIN MAURICE	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-67* is/are pending in the application.

4a) Of the above claim(s) *49 and 57-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-48 and 50-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 08, 2007 has been entered.

Applicant's response received on 09/24/2007 has been entered. Claims 1-42 were cancelled. Claims 43-67 are pending. Claim 43 was amended.

Claims 49 and 57-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 43-48 and 50-56 are currently under examination.

This application 10/520,745 filed on Aug. 22, 2005 is a 371 of PCT/GB03/03012 filed on 07/11/2003.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Previous rejection of claims 43-48 and 50-56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended.

The amended claim 43 has clarified the limitation "wherein the *passenger* peptide binding moiety is other than a chimeric or fusion protein" regarding in what sense the peptide-binding moiety is considered as a passenger. Specifically, the amended claim 43 now recites, "wherein the passenger peptide binding moiety is other than a chimeric or fusion protein and wherein said passenger peptide is other than one derived from the virus or said packing cell".

3. Claims 43-48 and 50-56 are *newly* rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by the claim amendments filed by Applicant on 09/24/2007.*

The amended claim 43 recites in step (i), "wherein said viral particle is enveloped using an envelope unable to naturally bind to cells of a species being targeted, *said viral particle in a first cell binding activity* wherein the viral packaging cell also contains nucleic acid encoding a passenger peptide binding moiety", which fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear what is encompassed by the phrase "*said viral particle in a first cell binding activity*" in term of what it means by the term "*in a first cell binding activity*". The phrase lacks a verb.

The amended claim 43 also recites in step (ii), "expressing the viral nucleic acid and nucleic acid encoding the passenger peptide binding moiety and incorporating said passenger peptide binding moiety into said packaging cell membrane so that a viral particle buds from said packaging cell membrane and the passenger peptide binding moiety is provided at a cell membrane such that the passenger peptide binding moiety is incorporated into the viral particle

to modify its first cell binding activity, wherein the passenger peptide binding moiety is other than a chimeric or fusion protein and wherein said passenger peptide is other than one derived from the virus or said packaging cell", which fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There are two issues with this limitation. First, it is unclear whether the limitation "incorporating said passenger peptide binding moiety into said packaging cell membrane" is the result of "expressing the viral nucleic acid and nucleic acid encoding the passenger peptide binding moiety". The limitation as written reads on two independent events: "expressing the viral nucleic acid and nucleic acid encoding the passenger peptide binding moiety" and "incorporating said passenger peptide binding moiety into said packaging cell membrane". For instance, it is unclear whether the nucleic acid encoding the passenger peptide binding moiety is being engineered as part of the genome of the recited viral particle or recited packaging cell or as an extrachromosomal nucleic acid. Second, the newly added limitations: "incorporating said passenger peptide binding moiety into said packaging cell membrane" and "wherein said passenger peptide is other than one derived from the virus or said packaging cell" appear to contradict to each other. It is unclear how the recited passenger peptide-binding moiety is incorporated into the packaging cell membrane, and at the same time, the passenger peptide is not considered as derived from the packaging cell. It is unclear, if the passenger peptide is neither derived from the cell or the virus, from where the passenger is actually derived.

Claims 44-48, and 50-56 depend from claim 43.

Claim Rejection – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 43-48 and 50-56 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a retroviral particle having a modified cell binding activity, comprising the steps of providing a retroviral packaging cell, wherein the retroviral packaging cell contains viral nucleic acid encoding an enveloped viral particle that is unable to naturally bind to a target cell; and transfecting said retroviral packaging cell line with an expression vector comprising a heterologous nucleic acid sequences encoding membrane bound human stem cell factor (mbSCF) operably linked to an eukaryotic promoter such that human mbSCF is expressed on the membrane of the packaging cell wherein a resulting retroviral particle produced from said packaging cell bears human mbSCF on the envelope of the retroviral particle that directs the binding of the retroviral particle to a target cell expressing c-kit on the membrane of said target cell, **does not** reasonably provide enablement the said method for **(i)** a nucleic acid encoding any peptide binding moiety other than human stem cell factor (SCF), or **(ii)** any target cell other than the target cell expressing c-kit receptor on its cell membrane, or **(iii)** a method comprising steps of making a retroviral particle having a modified cell binding activity, wherein the modified cell binding activity of said retroviral particle is determined by any non-Envelope-receptor interactions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Previous rejection is ***maintained*** for the reasons of record advanced on pages 6-13 of the office action mailed on 09/05/2006. It is noted that, upon further consideration, the Examiner has broadened the enabled scope encompassed by the claims. More specifically, limitation of the enabled scope to megakaryoblastic leukemia cell line, have been withdrawn.

The issues contributing to the lack of predictability revealed in the prior arts and identified in the Non-Final rejection mailed on 09/05/2006 include (a) the size limitation and resulting intracellular location of any given passenger peptide binding moiety (including a non-cell membrane bound peptide) other than human SCF that can be expressed from the packaging cell such that the passenger peptide binding moiety is incorporated into the envelope of a given retroviral particle, (b) cross interaction between a passenger peptide binding moiety and a receptor affecting recited altered tropism of a viral particle, a process involving the topology and expressed levels of the introduced passenger peptide binding moiety in the viral envelope and the topology and expressed levels of its corresponding receptor(s) present on the cell surface under a given growth condition, (c) viral tropism determined by contacts between viruses and cell occur outside of the *bona fide* Env-receptor interaction, and (d) potential immune and inflammation responses as a result of introduced passenger peptide binding moiety and cell-derived components being concentrated along with viral vector particle.

Issues of unpredictability related to (a) and (b) are relevant to why specific interaction between the passenger peptide incorporated into the viral envelope and the receptor on the target cell is required to overcome the breadth of the claims relevant to **(i)** and **(ii)** (see enabled scope set forth above). The issue (c) is directly relevant to why *bona fide* Env-receptor interaction contributing to the viral tropism renders the claimed method as listed in the rejection of said

method **(iii)** considered not enabled for the methods. In this regard, as discussed on page 11 of Non-Final office action mailed on 09/05/2006, how a virus infects its host cell is determined by many factors including, but not limited to, the interactions between viral envelope proteins and receptor/co-receptor proteins on cell surface. Manel et al. reviewed the HTLV-1 tropism and envelope receptor stated, " --- tropism depends on many parameters that are independent of Env-receptor interactions, ---" (page 6022, right column, three paragraph under Conclusions and perspectives, Manel et al., HTLV-1 tropism and envelope receptor. *Oncogene.* 24(39): 6016-25, 2005). For instance, "contacts between viruses and cell also occur outside of the *bona fide* Env-receptor interactions that lead to productive viral replication" (page 6016, right column, second paragraph, Manel et al., HTLV-1 tropism and envelope receptor. *Oncogene.* 2005 24(39): 6016-25, 2005). Issue (d) is relevant to the rejection of said method (i), (ii), and (iii).

Applicant's Arguments

With respect to the aspect of the rejection regarding the breadth of the claims of a method of making a viral particle having a modified cell binding activity, Applicant's arguments filed on 09/24/2007 has focused on the abovementioned issue (d). No specific arguments pertaining to issues (a), (b) and (c) were presented in Applicant's arguments filed on 09/24/2007.

With regard to issue (d) potential immune and inflammation responses as a result of introduced passenger peptide binding moiety and cell-derived components being concentrated along with viral vector particle, Applicant argues that the working of instant invention would not necessarily be influenced by an immune response, and the presence of data for enveloped retroviruses that does not appear to have been affected by an immune response demonstrates that

other enveloped viruses would similarly be capable of functioning. Applicant also argues that various viruses have been used in gene therapy work including retroviruses, adenoviruses, adeno-associated viruses and herpes simplex viruses, the immunogenicity of the viruses and their envelopes are comparable in that work as in the current invention. The only key difference in the possible immunogenicity of the virus particles of the current invention is the passenger peptide. A skilled artisan seeking to include a passenger peptide in a virus particle surface will previously have investigated that peptide by itself including potential immunogenicity. Accordingly, one skilled in the art would appreciate that highly immunogenic peptides could potentially still be immunogenic when displayed on a virus particle envelope. There is nothing unexpected regarding potential immune responses to virus particles and furthermore, such an immune response does not influence whether the invention is enabled for any virus or passenger peptide.

Response to Applicant's Arguments

Applicant's arguments filed 09/24/2007 have been fully considered but they are not persuasive because of the reasons discussed below.

Since no specific arguments pertaining to issues (a), (b) and (c) were not documented in Applicant's arguments filed on 09/24/2007, the previous scope of enablement rejection relevant to these aspects are ***maintained*** for the reasons of record advanced on pages 6-13 of the Non-Final office action mailed on 09/05/2006.

With regard to issue (d), potential immune and inflammation responses as a result of introduced passenger peptide binding moiety and cell-derived components being concentrated along with viral vector particle, as discussed on page 11 of the Non-Final office action mailed on 09/05/2006, **Cronin et al.** stated, one problem with the methods outlined is that cell-derived

components are concentrated along with the vector particles leading to potential immune and inflammation responses (See page 390, second paragraph, Cronin et al., Altering the tropism of lentiviral vectors through pseudotyping. *Curr Gene Ther.* 5(4): 387-98, 2005; this reference has been cited in the Non-Final office action mailed on 09/05/2006). This issue is of particular relevance with respect to the incorporation of a cellular protein, a passenger peptide-binding moiety, into a viral particle that is regarded as the novelty of the instant application. How a viral particle incorporates, by budding, a desired passenger peptide binding moiety, which is engineered to be expressed in a packaging cell line, could vary depending on the peptide binding moiety of interest, the expression level of the peptide binding moiety of interest, and the particular viral particle and packaging cell line being considered. It is also worth noting that the claimed passenger peptide of instant application is not covalently linked to the existing viral envelope protein, rather the passenger protein is associated with (or incorporated into) the viral particle in the process of budding. The intrinsic characteristics of the passenger peptide (for instance, hydrophobic versus hydrophilic) would determine the affinity between the passenger peptide and the viral particle, and the duration the passenger peptide associated with the viral particle. The passenger peptide could dissociate with the viral particle at any time after budding, which would defeat the effort for making a viral particle having a modified cell binding activity. Moreover, the dissociated passenger peptide become readily available as an antigen to be presented to the immune system leading to immune response in the desired target cells of the host in a gene therapy setting. Even in the case that the passenger peptide is very hydrophobic and being incorporated into a viral particle as a structural constituent of the viral envelop proteins (in a non-fusion manner), **Gritsun et al.** reported that the variable domains of the

flavivirus envelope proteins reflect the antigenicity of the viral particle and may determine the pathogenesis of the viral particle because mutant viruses with altered tropisms and capacity of escaping immuno-neutralization harbor mutations within the variable clusters of envelop proteins (See abstract and Figure 1, Gritsun et al., Analysis of flavivirus envelope proteins reveals variable domains that reflect their antigenicity and may determine their pathogenesis, *Virus Res.* 35(3): 307-21, 1995).

Relevant to the effect of altered envelope protein on the infectivity (i.e. targeting to a cell) of an enveloped viral particle, **Hayasaka et al.** demonstrated that the amino acid substitution E-S (40)-->P at position 40 in the envelope (E) glycoprotein was responsible for plaque size reduction, reduced infectious virus yields in cell culture and reduced mouse neurovirulence (See abstract and Figures 3 and 4, Hayasaka et al., Amino acid changes responsible for attenuation of virus neurovirulence in an infectious cDNA clone of the Oshima strain of tick-borne encephalitis virus, *J Gen Virol.* 85(Pt 4): 1007-18, 2004). However, it is unpredictable how a mutation in the envelope would affect the infectivity of an enveloped viral particle. Along the same line, it is unpredictable with regard to how a passenger peptide incorporated into the envelope of a viral particle would affect the infectivity of the viral particle. Thus, with the exception of use of SCF as a passenger peptide to target a retrovirus to cells expressing c-kit, as taught by the specification and supported by the art (See Applicant's own publication, Chandrashekran et al., Growth factor displayed on the surface of retroviral particles without manipulation of envelope proteins is biologically active and can enhance transduction, *J Gene Med.* 6(11): 1189-96, 2004), it would be unpredictable whether any passenger peptide

other than membrane-bound form of human stem cell factor (mbSCF) would be effective in modifying the effective tropism of a retroviral particle without undue experimentation.

In conclusion, the specification as filed fails to provide any specific guidance and/or working examples, regarding non-retroviral particles. The specification also fails to direct the skilled artisan to any teachings on the relationship between the control of the expression level of a passenger peptide binding moiety and its incorporation into viral particles, and how the relationship may affect the recognition between a passenger peptide and its receptor, and the infectivity the viral particles to specific target cells, which would allow one of skill in the art to make and use the claimed invention without undue experimentation. In view of the state of the unpredictability in the art, and the lack of guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to practice the breadth of the claimed invention. It is noted that Applicant failed to address other aspects of the enablement rejection except non-retroviral vector. Therefore, the rejection with respect to the issues (a) the size limitation and resulting intracellular location of any given passenger peptide binding moiety (including a non-cell membrane bound peptide) other than human SCF that can be expressed from the packaging cell such that the passenger peptide binding moiety is incorporated into the envelope of a given retroviral particle, (b) cross interaction between a passenger peptide binding moiety and a receptor affecting recited altered tropism of a viral particle, a process involving the topology and expressed levels of the introduced passenger peptide binding moiety in the viral envelope and the topology and expressed levels of its corresponding receptor(s) present on the cell surface under a given growth condition, (c) viral tropism determined by contacts between

viruses and cell occur outside of the *bona fide* Env-receptor interaction, are maintained for reasons of the record.

Claim Rejection – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 43-46 and 54-56 remain rejected under 35 U.S.C. 102(b) as being anticipated by Soong et al. (Soong et al., Molecular breeding of viruses. 25(4): 436-9, 2000). Applicant's arguments filed on 09/24/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 8-9 of the previous office action mailed on 06/05/2007, and summarized below.

Soong et al. teach a method molecular breeding of viruses, including retrovirus (which reads on an enveloped viral particle recited in claim 43 of instant application), with altered tropism without involving generation of fused viral envelope protein. Specifically, Soong et al. teach *in vitro* process of DNA shuffling (molecular breeding) mimics this mechanism on a vastly parallel and accelerated scale. Multiple homologous parental sequences are recombined in parallel, leading to a diverse library of complex recombinants from which desired improvements can be selected. Different proteins and enzymes have been improved using DNA shuffling. Soong et al. performed the first application of molecular breeding to viruses. A single round of

shuffling envelope sequences from six murine leukemia viruses (MLV) followed by selection yielded a clone with a completely *new tropism* for Chinese Hamster Ovary (CHOK1) cells (See abstract, Figure 3, Soong et al., 2000).

Applicant's arguments are based on that claim 43 has been amended to specify that the passenger peptide is a heterologous peptide, i.e., one not derived from the virus or packaging cell in which it is to be displayed. Thereby, Applicant argues that Soong et al. do not teach that a passenger peptide is not a viral envelope protein (either natural or mutated). Accordingly, Applicant argues that Soong et al. cannot anticipate the newly added limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell".

In response to Applicant's arguments, it is noted that, as discussed in the new rejection of claims 43-48 and 50-56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, the amended limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" appears to be in direct contradiction with the newly amended limitation "incorporating said passenger peptide binding moiety into said packaging cell membrane" recited in step (ii) of claim 43. As a result, the metes and bounds of either one of the two limitations cannot be determined when the other limitation is also considered.

Since the metes and bounds of the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" cannot be determined, the broadest and reasonable interpretation of the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" reads on any peptide that is not in the context of a given endogenous protein present in a given virus or in a given packaging cell. In other words,

the limitation essentially reads on any peptide becasue any given peptide can be considered as not derived from (i.e., not in the context of) a given reference viral or a given cellular protein. Under this interpretation, the limitation certainly reads on various envelope proteins encoded by the viral nucleic acid during the molecular breeding process taught by Soong et al. Moreover, the method taught by Soong et al. doesn't involve chimeric or fusion envelope proteins, and the altered tropism is a result of accelerated evolution of existing viral envelope proteins through recombination.

Thus, Soong et al. clearly anticipates claims 43-46 and 54-56 of instant application.

Claim Rejection – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 43, 48, 50 and 51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al. (Soong et al., Molecular breeding of viruses. *Nature* 25(4): 436-9, 2000) taken with Dropulic et al. (U.S. patent No. 6,114,141, issued Sep. 5, 2000; listed in the PTO-892 in Non-Final rejection mailed on 09/05/2006). Applicant's arguments filed on 09/24/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 10-12 of the previous office action mailed on 06/05/2007.

Applicant's arguments are based on that independent claim 43 has been amended to specify that the passenger peptide is incorporated into the packaging cell membrane. Furthermore, as discussed before, Applicant argues that Soong et al. do not describe the passenger peptide as being heterologous. Applicant also argues that Dropulic et al. do not describe the expression of such heterologous proteins so as to be incorporated into the viral particle via the envelope. Applicant further argues that the use of recombination in gene therapy vectors is not viable ("completely taboo", as phrased by Applicant) on the basis that it is not desirable to have gene therapy vectors recombining to each other.

In response to Applicant's arguments, it is noted that, again, as discussed in the new rejection of claims 43-48 and 50-56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, the amended limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" appears to be in direct contradiction with the newly amended limitation "incorporating said passenger peptide binding moiety into said packaging cell membrane" recited in step (ii) of claim 43. As a result, the metes and bounds of either one of the two limitations cannot be determined when the other limitation is also considered.

Since the metes and bounds of the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" cannot be determined, the broadest and reasonable interpretation of the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" reads on any peptide that is not in the context of a given endogenous protein present in a given virus or in a given packaging cell. In other words,

the limitation essentially reads on any peptide becasue any given peptide can be considered as not derived from (i.e., not in the context of) a given reference viral protein or a given reference cellular protein. Under this interpretation, the limitation certainly reads on various envelope proteins encoded by the viral nucleic acid during the molecular breeding process taught by Soong et al.

For the same reason discussed above, since the metes and bounds of the limitation "incorporating said passenger peptide binding moiety into said packaging cell membrane" cannot be determined, the broadest and reasonable interpretation of the limitation "incorporating said passenger peptide binding moiety into said packaging cell membrane" reads on any peptide because the limitation reads on any exogenous *in vitro* synthesized peptide being added to a virus infected packaging cell culture.

With regard to the arguments pertaining to the teachings by Soong et al. on the generation of retroviral vectors with altered tropisms by accelerated *in vitro* evolution via recombination, it is noted that Soong et al. *did not* teach the end products (retroviral vectors with altered tropisms) of *in vitro* evolution are to be used *together* for gene therapy purposes. Rather each one of the retroviral vectors with altered tropisms can be used independently based on the characteristics of desired target cells. It is also worth noting that the claimed method of making a viral particle having modified cell-binding activity (claim 43) and the claimed viral particle having modified cell-binding activity do not recited any limitation directing to gene therapy. Gene therapy is the intended use of the claimed vectors, and the intended use of a product is given limited, if any, patentable weight.

Therefore, the rejection of claims 43, 48, 50 and 51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al., 2000 taken with Dropulic et al. 2000 is ***maintained*** of the record, and reiterated below.

The teachings by Soong et al. and the interpretation of the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" have been discussed in the preceding section on the rejection of claims 43-46 and 54-56 under 35 U.S.C. 102(b) as being anticipated by Soong et al. 2000.

However, Soong et al., do not teach additional nucleic acid which can express any one of the bioactive agent selected from ricin, tumor necrosis factor, interleukin-2 (a cytokine), interferon-gamma, ribonuclease, deoxyribonuclease, pseudomonas exotoxin A and caspase.

With regard to claim 43, 48, 50 and 51, Dropulic et al. teach methods to express genes from viral vectors (See title and abstract). Specifically, Dropulic et al. teach the expression of antiviral agent including a cytokine, a single-chain antibody, a cellular antigen or receptor (See claims 4 and 21).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Soong et al. on the method of generating a virus with altered tropism and the teachings of Dropulic et al. on expressing a cytokine (interleukine-2) from a viral vector as taught by Dropulic et al. to achieve the claim 51 of instant application on a method of making a viral particle having a modified cell binding activity and also expressing a bioactive agent including interleukin-2.

One having ordinary skill in the art would have been motivated to modify the retroviral vector by the teachings of Soong et al. to express antiviral agent interleukin-2 by the teachings of

Dropulic et al. to achieve the goal of site specific delivery of interleukin as an antiviral agent via the selection of altered tropism of viral particle.

There would have been a reasonable expectation of success given (1) the generation of viral particle with altered tropism resulting from accelerated evolution of envelope genes by the teachings of Soong et al., and (2) the expression of a cytokine from a viral vector by the teachings of Dropulic et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

7. Claims 43, 48, 52 and 53 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al. (Soong et al., Molecular breeding of viruses. 25(4): 436-9, 2000) taken with Guber et al. (U.S. patent No. 569,177, issued Nov. 25, 1997; listed in the PTO-892 in Non-Final rejection mailed on 09/05/2006). Applicant's arguments filed on 09/24/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 12-14 of the previous office action mailed on 06/05/2007.

Applicant's arguments and Examiner's **Response to Applicant's arguments** are essentially the same as discussed in the preceding section of the rejection of claims 43, 48, 50 and 51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al., 2000 taken with Dropulic et al. 2000.

Accordingly, claims 43, 48, 52 and 53 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al., 2000 taken with Guber et al., 1997 is ***maintained*** of the record and reiterated below.

The teachings by Soong et al. and the interpretation of the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" have been discussed in the preceding section on the rejection of claims 43-46 and 54-56 under 35 U.S.C. 102(b) as being anticipated by Soong et al. 2000.

However, Soong et al., do not teach additional nucleic acid which can express any one of the bioactive agent, which is an enzyme, including thymidine kinase and cytosine deaminase, capable of converting a relatively non-toxic pro-drug into a cytotoxic drug.

With regard to claims 43, 48, and 52-53, Guber et al. teach recombinant retroviruses expressing a protein that converts a pro-drug into a cytotoxic agent (See title and abstract). Specifically, Guber et al. teach the expression of a nucleoside kinase thymidine kinase (See claims 6-8, 22-23) that converts a purine-based or pyridimine-based drug with little or no cytotoxicity into a cytotoxic drug (See claim 5)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Soong et al. on the method of generating a virus with altered tropism and the teachings of Guber et al. to express a thymidine kinase that converts a pro-drug into a cytotoxic drug to achieve the claims 52 and 53 of instant application regarding a method of making a viral particle having a modified cell binding activity and also expressing a bioactive agent such as thymidine kinase capable of converting a relatively non-toxic pro-drug into a cytotoxic drug.

One having ordinary skill in the art would have been motivated to modify the retroviral vector by the teachings of Soong et al. to express thymidine kinase by the teachings of Guber et al. to achieve the goal of site specific delivery of thymidine kinase to a desired cell target for

converting a pro-drug into a cytotoxic drug via the binding specificity of altered tropism of virus as taught by Soong et al.

There would have been a reasonable expectation of success given (1) the generation of viral particle with altered tropism resulting from accelerated evolution of envelope genes by the teachings of Soong et al., and (2) the expression of thymidine kinase converting a pro-drug into a cytotoxic drug from a recombinant retroviral vector by the teachings of Guber et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

8. Claims 43 and 47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al. (Soong et al., Molecular breeding of viruses. 25(4): 436-9, 2000) taken with Yajima et al. (Retroviral vector targeting human cells via c-Kit-stem cell factor interaction. *Hum Gene Ther.* 9(6): 779-87, 1998; listed as the last reference in the IDS filed on 05/04/2007). Applicant's arguments filed on 09/24/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 14-16 of the previous office action mailed on 06/05/2007.

Applicant's arguments regarding the deficiency of Soong et al., 2000 pertaining to the newly added limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" has been discussed in the preceding section on the rejection of claims 43-46 and 54-56 under 35 U.S.C. 102(b) as being anticipated by Soong et al., 2000. Applicant also argues that Yajima et al. do not describe enveloped viruses containing heterologous peptides derived from packaging cells at all, but describes a chimeric protein to a non-chimera and it is

therefore believed that one skilled in the art would not be led to combine these documents nor would such a combination remove an inventive step from the present claims.

Examiner's response to Applicant's arguments regarding the deficiency of Soong et al., 2000 pertaining to the newly added limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" has been addressed in the preceding section on the rejection of claims 43-46 and 54-56 under 35 U.S.C. 102(b) as being anticipated by Soong et al., 2000. With regard to the arguments Yajima et al. do not describe enveloped viruses containing heterologous peptides derived from packaging cells at all, it is noted that Yajima et al. was cited for the limitation of claim 47 (which depends from claim 43) of instant application because of its teachings of engineering a recombinant retroviral vector that can target human cells expressing a c-Kit receptor via a ligand-receptor interaction. Specifically, the ligand is a stem cell factor (SCF), which interacts with c-Kit receptor.

Accordingly, claims 43 and 47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Soong et al., 2000 taken with Yajima et al., 1998 is ***maintained*** of the record and reiterated below.

The teachings by Soong et al. and the interpretation of the limitation "wherein said passenger peptide is other than one derived from the virus or said packaging cell" have been discussed in the preceding section on the rejection of claims 43-46 and 54-56 under 35 U.S.C. 102(b) as being anticipated by Soong et al. 2000.

However, Soong et al., do not teach the introduced peptide binding moiety being membrane bound stem cell factor as recited in claim 47 of instant application.

With regard to claims 43 and 47, Yajima et al. teach engineering a recombinant retroviral vector that can target human cells expressing a c-Kit receptor via a ligand-receptor interaction. Specifically, the lined is a stem cell factor and the receptor is c-Kit receptor.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Soong et al. on the method of generating a virus with altered tropism and the teachings of Yajima et al. on a recombinant retroviral vector that can target human cells expressing a c-Kit receptor via a ligand-receptor interaction to achieve the claims 42 and 47 of instant application regarding a method of making a viral particle having a modified cell binding activity and expressing a membrane bound stem cell factor.

One having ordinary skill in the art would have been motivated to modify the retroviral vector by the teachings of Soong et al. and express stem cell factor by the teachings of Yajima et al. to achieve the goal of targeted gene transfer into stem cell, such as hematopoietic stem cells, by retroviral vectors to facilitate the development of in vivo strategies for stem cell gene therapy via the binding specificity of altered tropism of virus as taught by Soong et al.

There would have been a reasonable expectation of success given (1) the generation of viral particle with altered tropism resulting from accelerated evolution of envelope genes by the teachings of Soong et al., and (2) a recombinant retroviral vector that can target human cells expressing a c-Kit receptor via a ligand (SCF)-receptor (C-Kit) interaction by the teachings of Yajima et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

9. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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